



REVIEW

Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit [version 1; referees: 2 approved]

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Abstract

This is a review of hypnotic drug risks and benefits, reassessing and updating advice presented to the Commissioner of the Food and Drug Administration (United States FDA). Almost every month, new information appears about the risks of hypnotics (sleeping pills). This review includes new information on the growing USA overdose epidemic, eight new epidemiologic studies of hypnotics' mortality not available for previous compilations, and new emphasis on risks of short-term hypnotic prescription. The most important risks of hypnotics include excess mortality, especially overdose deaths, quiet deaths at night, infections, cancer, depression and suicide, automobile crashes, falls, and other accidents, and hypnotic-withdrawal insomnia. The short-term use of one-two prescriptions is associated with greater risk per dose than long-term use. Hypnotics are usually prescribed without approved indication, most often with specific contraindications, but even when indicated, there is little or no benefit. The recommended doses objectively increase sleep little if at all, daytime performance is often made worse, not better, and the lack of general health benefits is commonly misrepresented in advertising. Treatments such as the cognitive behavioral treatment of insomnia and bright light treatment of circadian rhythm disorders might offer safer and more effective alternative approaches to insomnia.

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Competing interests: Since 1979 publication of hypnotics' epidemiology from the American Cancer Society CPSI study, the author has been a frequent critic of hypnotics risks and benefits, especially through his non-profit internet web site, www.DarkSideOfSleepingPills.com, that offers readers additional information and references about hypnotics. Dr. Kripke's family owns non-controlling stock and options in a large conglomerate that in turn invested a tiny percentage of its capital in Sanofi-Aventis and Johnson and Johnson stock. The author has advised the USA Food and Drug Administration to take certain actions regarding hypnotics (Petition available at <http://www.regulations.gov/#!docketDetail;D=FDA-2015-P-3959>), and related litigation may arise. The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, other stock ownership or options, expert testimony, grants or patents received or pending or royalties. No writing assistance was utilized in the production of this manuscript.

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Introduction

This is a reassessment of hypnotic drug risks and benefits, updating and expanding information presented October 26, 2015 to the Commissioner of the Food and Drug Administration (United States FDA) as part B of Petition FDA-2015-P-3959, accessible in April, 2016 at <http://www.regulations.gov/#!docketDetail;D=FDA-2015-P-3959> along with Comments responding to that Petition. Almost every month, new information about the risks of hypnotics (sleeping pills) appears. This review includes new information on the growing overdose epidemic, eight new epidemiologic studies of hypnotics' mortality risk not available for previous analyses, and new emphasis on risks of short-term hypnotic usage.

Risks of hypnotic drugs

Hypnotic drugs increase all-cause mortality

Use of hypnotic drugs is associated prospectively with a greatly increased risk of all-cause mortality. Some of this mortality has been documented as deaths caused by hypnotics by Medical Examiners, attributed to respiratory arrests resulting from "overdose." However, it is likely that many deaths from respiratory depression occur among patients never seen by coroners, especially when the death is caused by a combination of hypnotics with other contributing factors, so that the lethal hypnotic dosage may by itself have been within currently-customary dosage ranges. In addition to respiratory depression, hypnotics appear to be causally related to serious illnesses and premature deaths from cancer, serious infections, mood disorders, accidental injuries, suicides and homicides.

The overdose epidemic

Only a small fraction of U.S. deaths has been examined by coroners and Medical Examiners. Thus, it is commonly assumed that overdose deaths have been grossly under-reported. Despite such underestimation, U.S. drug and opioid overdose deaths reported in 2014 reached 47,055, a 137% increase since 2000¹. Likewise, U.S. use of hypnotics has dramatically increased over about the same interval². Available death certificate reports seem unclear, but perhaps one third of death certificates listing overdose with an opiate as a cause of death also lists a benzodiazepine, Z hypnotic, or barbiturate as a cause of death (retrieved from CDC Wonder). An opioid prescription is more likely to lead to overdose when a hypnotic is prescribed³. There have also been several thousand yearly reported overdoses involving a hypnotic in which an opiate was not involved. So great is the recent increase in overdose deaths that it has lowered overall life expectancy in much of the U.S. adult population^{4,5}. Overdoses kill more Americans than automobile accidents or murders. Aside from overdose deaths, benzodiazepines were involved in a comparably increasing number of emergency room visits over a similar time interval, and over half of these also involved opioids, alcohol, or all three in combination⁶. Combined overdoses of opiates and benzodiazepine agonists had more severe outcomes. A recent *JAMA Psychiatry* Viewpoint gave an even larger estimate of self-injury deaths often due to drug intoxication at 68,298 for 2013, and that did not include the role of suicidally-motivated dangerous driving⁷. Suicides from all causes per capita have been increasing, particularly among women, and particularly in recent years at about the time that generic zolpidem became available⁸. Hypnotics are a factor in more than half of intoxication and dangerous driving deaths⁹.

Forty epidemiologic studies

In 40 epidemiologic studies that provided comparable risk ratios for mortality associated with hypnotics, 39 showed that hypnotics were associated with excess mortality, as listed in the [Appendix](#). One exception was a small study by Merlo *et al.* that nevertheless found hypnotics associated with cancer deaths¹⁰. A partial exception was a study from Taiwan that found benzodiazepine hypnotics associated with significant excess mortality, but found zolpidem 10 mg associated with significantly reduced mortality in adjusted models, despite a significantly-increased unadjusted mortality risk for zolpidem and a significantly-increased adjusted risk of cancer mortality for zolpidem¹¹. In a comment to this report appearing with it on the internet, I have questioned the statistical methods of adjusting zolpidem risks¹¹.

Only this one of the 40 epidemiologic studies of hypnotic drugs reported any association with improved patient survival, and that only after questionable statistical adjustments¹¹. None of the other 39 studies found hypnotic drug risk ratios significantly less than 1.0. That is, in 39 studies there was no evidence that hypnotics ever benefit patient survival. To find 39 of 40 studies showing a positive risk ratio was very highly significant, $P < 0.000001$. Also, the evidence of association satisfied all nine Bradford Hill criteria for inferring causality¹², though skepticism despite meeting these criteria may be warranted¹³. There remain questions concerning the magnitude of the causality. The randomized placebo-controlled trials I have suggested would help clarify this causality magnitude¹².

Of the 40 epidemiologic studies, 31 individual studies reported statistically significant mortality odds ratios, risk ratios, or hazard ratios exceeding 1.0. All 18 studies reporting on samples of >14,000 people found significant mortality risks, but nine of 22 smaller studies found positive trends that were not significant. Most of the non-significant reports were among the earliest 15 published before 2006. Of studies analyzing follow-ups of 8 years or less, 22 of 26 studies reported a significant association, but of studies with longer follow-ups, only 10 of 14 studies observed significant mortality risks. This may suggest that during long prospective follow-ups, many patients initially taking hypnotics will discontinue hypnotic usage, whereas many controls not using hypnotics at prospective baseline may have begun using hypnotics during a long follow-up, so that the longer the follow-up, the more mixing of hypnotic-consuming and control groups becomes likely. Mixing weakens the risk-ratio contrasts observed. In long follow-ups, one is also studying the selected survivors of the more marked short-term risks that have been recently described^{14,15}.

Most of the 40 studies reported mortality risk ratios of less than 1.5, but some of the highest quality studies reported among the highest risk ratios. Four of the most recent studies were particularly persuasive, as presented below.

The Geisinger Health System study

From electronic records of the Geisinger Health System in Eastern Pennsylvania, a sample of 34,205 patients was drawn with carefully controlled 2:1 matching of hypnotic users with non-user controls for age, gender, smoking, and various comorbidities. Compared to a reference hazard ratio of 1.0 for non-users of hypnotics, the

fully-adjusted mortality hazard ratio for use of 0.4–18 hypnotic doses per year was 3.60 (2.92–4.44, 95% CI), for those using 18–132 doses per year, the hazard ratio was 4.43 (3.67–5.36), and for >132 doses per year, the hazard ratio was 5.32 (4.50–6.30)¹⁶. Each of these associations was significant with $P < 0.001$. Sensitivity studies showed that little of the hypnotic-associated mortality could be explained by known confounders or use of hypnotics before commencement of the study. In this sample, prescriptions for each of the following drugs were found to significantly predict increased mortality with statistical significance: zolpidem, temazepam, eszopiclone, zaleplon, triazolam, flurazepam or quazepam, and barbiturates prescribed to induce sleep. This review is principally concerned with these popular hypnotics for which drug-specific mortality data are available. Barbiturates prescribed at night for sleep considered as a group had about the same empirical hazard ratios as the benzodiazepines and zolpidem, but the observed hazard ratio for eszopiclone was significantly higher than that of barbiturates, possibly biased by the shorter average follow-up intervals for this more-recently introduced drug¹⁶.

The Weich *et al.* study

In a sample of over 100,000 hypnotic users and matched controls from the representative British General Practice Research Database¹⁷, users of 1–30 defined daily doses (DDD) of hypnotics and anxiolytics within a year had fully adjusted dose-responsive mortality hazard ratios of 2.55 (2.42–2.69, 95% CI) for 1–30 DDD (defined daily doses in the first year); 3.78 (3.54–4.04) for 31–60 DDD, 4.19 (3.84–4.58) for DDD 61–90, and 4.51 (4.22–4.82) for DDD >90. Extensive full adjustment for potential confounders resulted in only very small and inconsistent decreases in the estimated hazard ratios, and many methodological details were focused on minimizing possibilities of confounding. Use of benzodiazepine hypnotics only was associated with higher hazard ratios than use of “Z” hypnotics only. These hazard ratios were remarkably similar to those from the Geisinger Health System, considering the many differences in drug characteristics, samples, design, confounder controls, and analyses. Note that as in the Geisinger Health System study, much of the mortality was associated with early deaths after limited doses of hypnotics, perhaps as little as one-two prescriptions filled or refilled.

Norwegian Pharmacy Database

A recent representative study of the Norwegian Pharmacy Database found that benzodiazepine-receptor-agonist use was associated with a mortality odds ratio of 2.30 (2.20–2.40)¹⁸. The authors argued that terminal illness caused an upturn in benzodiazepine-receptor agonist use shortly before death (which might be appropriate for hospice care), and therefore they argued that the increased benzodiazepine-agonist use among those who would die was demonstrated as a confound of terminal illness. To the contrary, their data demonstrated an excess of benzodiazepine use even among those who would not die until 22 months or later, so the benzodiazepine use of this population was elevated before the terminal upturn in hypnotic usage that the authors had demonstrated. Also, the upturn in death-associated hypnotic use 6–10 months before subsequent death might be consistent with a causal lethal hazard resulting from only a few short months’ exposures to hypnotics. The Norwegian Pharmacy Database did not enable this study to

identify terminal illnesses, to analyze comorbidities or to control for other confounders.

The Palmaro *et al.* study

In this large study, both French and British case-control samples were drawn from reasonably-representative national samples¹⁴. Results had many similarities to those of Weich *et al.*¹⁷ despite numerous differences in statistical design. Substantially lower overall hazard ratios were found in the French sample (not all significant after adjustment), perhaps because a large number of occasional users were included. An important finding was the much higher hazard ratios associated with the initial 3–6 months of hypnotics-benzodiazepines use, as high as 11.12 (95% CI, 9.91–12.47) for the 3-month analysis of the British sample. This sharpened the evidence, also noted in the three previous studies discussed, that although dose-response is observed over several years, much of the hypnotic-associated hazard is observed during the early months of usage after as little as one or two prescriptions.

It should be noted that Weich *et al.*¹⁷ and Palmaro *et al.*¹⁴ found significant hazard ratios associated with diazepam and other benzodiazepines that are not considered hypnotics (though tranquilizer benzodiazepines may often be used for sleep). These more modern data with better drug identification and measurements of prescriptions during follow-up must be considered more reliable, but neither “Valium” nor “Librium” had been associated with excess mortality in the previous large U.S. CPSII study¹⁹. One might argue that if diazepam has a different hazard from temazepam, for example, this specificity tends to bolster the evidence for causality with temazepam. On the other hand, it would not be clear if the specificity is in the drug’s pharmaceutical effects, in its absorption and half-life, in its usual time of administration, in other aspects of frequency and dosage of administration, or in various associated confounders.

Note that these epidemiologic studies had many limitations¹². However, the limitations that would tend to bias the results towards underestimating the associations of hypnotics and mortality appeared more influential than those that would bias towards overestimation of the risks. In particular, studies with the most careful efforts to control for confounders found that such control made little difference in the estimated risk ratios, but the hazard ratios in these carefully-controlled studies tended to be higher. The risk ratios derived, like the studies themselves, were extremely heterogeneous, probably due to differences in the size, age, gender, and ethnicity of samples and their health status, the nature of the hypnotics studied, the accuracy with which the drugs involved and their dosages were known, the control variables available, and the duration of follow-up observations to ascertain mortality. Meta-analyses attempting to group 40 such heterogeneous studies would not be clarifying.

Short-term hypnotic use is unsafe

Data provided by Palmaro *et al.*¹⁴ and Chung *et al.*¹⁵ expanded the hints in the other large epidemiologic studies^{16–18} that short-term hypnotic usage has surprisingly high risks: apparently short-term hypnotic use has higher risks than long-term usage on a per dose or per-unit-time basis. It is logical that for a patient with an “overdose” of common contributory factors such as aging, obesity, sleep apnea,

alcohol overuse, and opiate use, even a single hypnotic dose could be lethal on the first night of consumption. Depending on the drug and the patient's metabolic capacity, the hypnotic drug concentration in blood could increase for the first few consecutive nights of dosage, but eventually, developing tolerance might make each dose less risky among those who had survived the initial doses. There would continue to be deaths at a lower rate after tolerance develops because of hypnotic dose-escalation in response to tolerance, addition of other sedatives or opiates, especially-heavy pre-sleep alcohol consumption, body position, altitude, upper respiratory infections, and other contributing factors that could suddenly produce hypnotic lethality even after several years of steady consumption. In addition, new consumption of non-sedative drugs that impair liver drug metabolism and even foods such as grapefruit can suddenly make a patient more vulnerable to a customary dose. Understanding these considerations, limitation of hypnotic prescribing to a small number of doses or a single prescription cannot be considered safe.

Are insomnia and depression explanatory confounders?

Several reports carefully examined insomnia and depression as potential confounders of the association of hypnotics with mortality, finding that insomnia and depression could explain little if any of this association^{17,20–22}. Note also that the evidence does not permit us to assume that causality between insomnia, depression, and hypnotic usage is one-way when contemplating confounder control, as there is reverse causality^{23,24}.

Summary of mortality risk epidemiology

Altogether, the epidemiologic literature is conclusive that hypnotic use is associated with excess mortality. The better studies tend to show very high dose-response risk ratios suggesting association with a very large number of deaths. A supplement to the Geisinger Health System data showed that the risk ratios demonstrated lead to estimated U.S. deaths associated with hypnotic usage of the same order of magnitude as those associated with cigarette use, around 300,000–500,000 per year¹⁶. Evidence has been presented from several independent studies that most of these deaths cannot be attributed to known forms of confounding, and indeed, adjustment for the major confounders such as smoking and comorbidities produced little change in the estimated associations in most of these studies. Authors acknowledge that their estimates of adjusted association of hypnotics and mortality could be influenced by inadequate ascertainment of confounding factors or lack of control for a very large number of potential confounds with small or rare effects. It is because skeptics may question whether the strong associations of hypnotics with mortality are causal, despite data fulfilling the Bradford Hill criteria for inferring causality¹³, that large post-marketing controlled trials of vulnerable patients may still be needed¹².

Hypnotic drugs have a long history of delayed recognition of mortality risks

Despite its well-known risks of lethality, pentobarbital was nevertheless for decades a preferred hypnotic routinely prescribed for patients seeking sleep aids. In the U.S. today, the most notable human application of pentobarbital is in implementing the death sentence. Although it has been believed that the more modern benzodiazepine and benzodiazepine-receptor-agonist hypnotics

that replaced barbiturates have higher acute margins of safety and therefore lower risks than pentobarbital, death certificate and epidemiologic data do not confirm that the newer drugs are significantly safer than barbiturates in routine use^{12,25}.

Hypnotics produce an excess of deaths at night

In the first Cancer Prevention Study, the percentage of deaths at night were found to be increased by 15.6% among those taking hypnotics ($P=0.01$), presumably due to respiratory suppression²⁶. In that study, the higher percentage of excess deaths at night associated with taking hypnotics accounted for about one third of total excess mortality associated with hypnotics. These nocturnal deaths were attributed to other causes, even though quiet respiratory suppression as a cause would explain the higher percentage of nocturnal deaths observed among those taking hypnotics than among controls.

The mechanisms of dangerous hypnotic respiratory depression are well-understood. The common hypnotics including barbiturates, benzodiazepines, the “Z” drugs and other benzodiazepine-receptor agonists bind to gamma-aminobutyric acid (GABA) receptors. These ligands-agonists alter the configuration of the receptors to allow negative chloride ions to more readily enter the neurons, where the chloride negatively hyperpolarizes the membranes and inhibits the neurons from firing. When they depress neural respiratory center firing, such drugs can acutely suppress respiration and in large enough dosage, or when individuals are particularly sensitive, may effectively arrest respiration, which leads rapidly to cardiac arrest and consequent death^{25,27,28}. Respiratory depression is accordingly, and accurately, listed among zolpidem's warnings and precautions²⁹. The barbiturates and alcohol bind to different locations on GABA receptors, where they exert additive or perhaps synergistic respiratory depression effects which may add to benzodiazepine-agonist effects. An antihistamine, diphenhydramine, also binds to GABA_A receptors, but it does not seem known whether the actions of diphenhydramine on GABA receptors are similar to benzodiazepines. Opiates bind to mu (μ) opioid receptors on respiratory neurons, where they hyperpolarize neural membranes by opening potassium channels³⁰. Thus opiates, benzodiazepine agonists, and alcohol have additive or synergistic effects inhibiting respiratory neurons.

Hypnotics can cause serious and potentially lethal infections

A meta-analysis of available placebo-controlled randomized clinical trials showed that hypnotics cause infections ($p<0.00001$)³¹. Because these clinical trials randomized hypnotics versus placebos, the 44% higher infection rate among participants who were given hypnotics was proven to be caused by the hypnotics. Moreover, the lead manufacturer of zolpidem has acknowledged that zolpidem induces infections, based on that manufacturer's own clinical trials data³². The FDA also found dozens of reports of zolpidem-related severe infections among post-marketing reports²⁹.

Extensive epidemiologic data demonstrated that hypnotics are associated with increased pneumonia including fatal pneumonia³³. This finding was not confirmed by one Taiwanese study³⁴, but another Taiwanese study focusing on patients with sleep disturbances found that use of zolpidem was associated with 62%–91%

increased hospitalizations for serious infections³⁵. A Taiwan study of patients with chronic obstructive pulmonary disease found highly significant odds ratios associated with benzodiazepine use of 9.3 for pneumonia, 10.4 for acute chronic obstructive pulmonary disease (COPD) exacerbation, 45.0 for acute respiratory failure, and 18.6 for cardiopulmonary arrest; whereas the odds ratios for “Z” drugs such as zolpidem were of almost similar magnitude³. In confirmation, note in the Geisinger Health Study supplement, Table 7¹⁶, mortality hazard ratios were likewise specifically elevated among hypnotics users with COPD. Another Taiwanese study observed that use of zolpidem was associated with increased risk of pyogenic liver abscess³⁶. British data showed that use of benzodiazepines and use of the hypnotic zopiclone (containing 50% eszopiclone as the active ingredient) were significantly related to asthma exacerbation and to all-cause mortality following exacerbation³⁷. This asthma study described some of the benzodiazepine-agonist-mediated impairments of immune surveillance³⁷. Perhaps as a consequence of post-hospital continuation of benzodiazepines and resultant infection, use of benzodiazepines was associated with 23% increased hospital readmission in North Carolina³⁸. In summary, epidemiologic evidence indicates that hypnotics not only cause the mild upper-respiratory infections most commonly reported in available controlled clinical trials³¹, but also more severe and life-threatening infections. Since such infections demonstrably impair survival, infection is shown to be an additional mechanism by which hypnotics covertly increase mortality. The death certificate would be likely to list the infection as a cause of death but not the hypnotic which may have caused that infection.

Animal studies confirm that hypnotics can cause infections. A controlled trial demonstrated in mice that diazepam exacerbated *Streptococcus pneumoniae* infection through GABA_A receptors, partly explaining the underlying immune mechanisms³⁹. In mice, diazepam also exacerbated cowpox, a viral infection⁴⁰. Midazolam impaired equine immune responses, attributable to effects on macrophage peripheral benzodiazepine receptors (now called TSPO)⁴¹. Evidence for involvement of the peripheral benzodiazepine receptor TSPO in immune impairment also came from specific test compounds in mice⁴². Thus, hypnotic drugs cause increased risk of potentially lethal infections in controlled laboratory experiments.

Hypnotics are associated with increased cancer **Human clinical trials strongly suggested that hypnotics cause cancer**

A compilation of randomized controlled trials of hypnotics showed 12 cancers or tumors of uncertain malignancy reported among participants randomized to a hypnotic, but none (zero) among those randomized to placebo (P=0.032, two-tailed Fisher Exact Test)⁴³. When the FDA repeated this audit of their controlled trials data, they counted 13 cancers among those randomized to hypnotics versus none (zero) from placebo⁴³.

The controlled-trials compilations described above did not include indiplon, an unlicensed zaleplon-like benzodiazepine agonist and hypnotic, for which studies published subsequently indicated three incident cancers in the indiplon groups and none in the randomized control groups^{44,45}. The compilations did include cancers associated with the marketed hypnotic ramelteon that admittedly has a

very different molecular mode of action from the benzodiazepine agonists.

The FDA was not persuaded that these human controlled-trials data required regulatory action, because most of the definite cancers were only minor skin cancers, because of heterogeneities in the data, and because the cancers were recognized after such short randomization periods. Nevertheless, the controlled trials data suggested more than skin cancer. There were cancers of organs apart from skin noted among those treated with hypnotics but none among those randomized to placebo. Reconsideration of FDA’s deferral of action is now encouraged by new animal testing and new epidemiologic findings: over half of the research referenced in this manuscript appeared after that FDA deferral of action.

Because hypnotics seem to cause cancers to be suddenly recognized during short clinical trials, e.g., from one month to one year, the short-term effects are likely to arise more from hypnotics promoting progression of tiny pre-existing cancers rather than from effects upon microscopic cancer initiation. Such progression may cause a cancer death, whether or not the hypnotics initiated the cancer.

Animal studies proved that hypnotics cause cancer

The animal data in the FDA files for zolpidem indicated that increasing doses of zolpidem fed to rats resulted in increasing numbers of renal liposarcomas and lipomas combined (statistically significant). These data also showed increased thyroid follicular adenomas and carcinomas combined, and increased testicular interstitial cell adenomas, but the latter findings did not reach statistical significance⁴⁶. There were no such tumors – that is, zero tumors – in the placebo groups. These studies were too small, however, to have substantial power for these neoplasms. Expert FDA pharmacy examiners interpreted the data as suggesting an unknown degree of cancer risk for humans.

These experiments, which showed tumors resulting from feeding zolpidem to rats and suggested a dose-dependent relationship, apparently were never extended, clarified, published, or otherwise followed up.

Similarly, the animal data used for eszopiclone evaluation relied largely on old zopiclone data, since eszopiclone is roughly 50% of zopiclone, and eszopiclone is thought to be the active isomer. Along with other issues, the animal evidence that zopiclone caused animal cancers was of great enough concern to FDA’s scientists, that at least five FDA scientists and medical officers recommended against approval of eszopiclone⁴⁷. Tumors of the lung in rodents were of special concern; these findings also anticipated the human-specific association of hypnotics with lung and esophageal cancers, as will be described below. Eszopiclone was nevertheless approved as a hypnotic.

Since zolpidem and eszopiclone were evaluated, much additional evidence has appeared relating hypnotics to cancer. Amerio *et al.* systematically surveyed FDA records including much animal data not included in the earlier compilation of hypnotics trials and concluded that hypnotics and sedatives had among the most elevated cancer hazards among psychotropic drugs⁴⁸.

In vitro studies strongly suggest that hypnotics cause cancer

Zopiclone, zaleplon, and ramelteon are clastogenic^{47,49,50}. These hypnotics damage chromosomes. Clastogens are potentially mutagenic agents that induce disruption or breakages of chromosomes. This process can lead to carcinogenesis. Cells that are not killed by the clastogenic effect may become transformed to cancer⁵¹. One of the several formulations of zolpidem was said from *in vitro* studies not to be clastogenic⁵². Other than the four drugs mentioned, no information has been located that other hypnotic drugs found to be associated with cancer have ever been adequately tested for clastogenicity.

Clastogenicity is only one mechanism by which hypnotics are likely to be carcinogenic, through either initiating cancers or promoting progression through additional mutations of cancer cells, or both. The alterations of immune surveillance produced by benzodiazepine agonists, discussed in relation to infection above, suggest additional mechanisms by which cancer initiation and progression might be facilitated or disinhibited⁵³. Hypnotic-initiated increases in infections and consequent inflammation is another potential carcinogenic mechanism. These animal-demonstrated and *in-vitro* mechanisms for carcinogenicity of hypnotics, that have been widely ignored, support evidence that hypnotics cause human cancer.

Human epidemiology studies demonstrate elevated cancer incidence associated with hypnotics

A 2008 paper⁴³ listed three prior epidemiologic studies reporting associations of hypnotics with cancer deaths^{10,54,55}. Analysis of CPSII data found that the elevation in deaths associated with hypnotics was comparable to that associated with cigarettes⁵⁵, though not entirely due to cancer. The report of Merlo *et al.* was unique in that the small study showed significantly increased cancer deaths among hypnotic users, but the increase in overall deaths associated with hypnotics was not significant¹⁰. Mallon, Broman, and Hetta found a much higher cancer adjusted hazard ratio for habitual sleeping pill use of 5.3 (95% C.I. 1.8–15.4) than for smoking among males; none of the specific causes of death were individually significant among females⁵⁴. A similar result was shown in a later paper for males, but the simple significant mortality elevation of regular hypnotic use among females was lost after multivariate adjustment in the second study²¹. More recently, a number of new studies have appeared reporting that hypnotic usage is related to cancer incidence and mortality. Hartz and Ross found a significant association of hypnotic use with melanoma and close-to-significant associations for lung and breast cancers⁵⁶. Kao *et al.* found a remarkable 6.24 (4.13–9.43, 95% CI) hazard ratio for cancer incidence among those using at least 300 mg of zolpidem per year without other-benzodiazepine consumption (this would correspond to slightly more than one 5 mg dose per week)⁵⁷. In this Taiwanese national study, smoking and body mass index (BMI) were not controlled, but the overall cancer hazard ratios for zolpidem users were almost identical among men and women, despite an almost 11-fold greater prevalence of smoking among adult men compared to Taiwanese women at the time⁵⁸. BMI was not controlled, but at that time in Taiwan, although being overweight was more common among women, obesity was more common among men⁵⁹. In a complementary study of benzodiazepines in Taiwan, benzodiazepines were associated with a 1.19 (1.08–1.32 95% CI)

cancer incidence hazard ratio, with over twice the benzodiazepine-associated hazard among men as among women⁶⁰. Similarly, a brief analysis of the national data from Taiwan found a significant cancer adjusted odds ratio for two of three benzodiazepine hypnotics⁶¹.

In the Geisinger Health study using electronic medical records, Kripke *et al.* found a hazard ratio for cancer incidence of 1.35 (1.18–1.55 95% CI) associated with use of >132 hypnotic doses per year, with specific hazard ratios of 1.28 (1.03–1.59) for high-dose zolpidem and 1.99 (1.57–2.52) for high-dose temazepam¹⁶. There was a significant dose-response. This study was carefully controlled for age, gender, smoking, BMI, and by matching comorbidities among cases and controls. Jiao *et al.* found no excess of colorectal cancer among those reporting sleeping pill usage <3 times per week versus ≥3 times per week in the Women's Health Initiative data set⁶², a result consistent with the Hartz and Ross report on the same data set⁵⁶, but since the contrast of frequencies of usage was weak and the type and quantity of hypnotic consumption were not determined objectively, the negative observation was not very persuasive. We would not expect hypnotics to promote all cancers equally. Indeed, selective specificity among cancer types would be anticipated if the mechanisms are causal. Pottegard *et al.* and Sivertsen *et al.* found small but significant associations of hypnotic usage with cancer, especially lung cancer^{63,64}, but since they had not controlled for cigarette smoking, both groups thought their result might have arisen from confounding, albeit confounding was not conclusively demonstrated⁶⁵. That investigators failed to control for important confounders is not proof that confounding explains the significant hazard. Several U.S. and European groups^{63,64} and also Kao *et al.*⁵⁷ found high hazard ratios for lung and esophageal tumors, and the two San Diego studies had carefully controlled for smoking^{16,55}. We had proposed that effects of hypnotics on weakening the gastro-esophageal sphincter and permitting more gastro-esophageal regurgitation⁶⁶ might account for the high cancer-specific rates of esophageal and lung tumors¹⁶. These multiple studies finding hypnotics associated with human lung cancer were consistent with concerns of FDA scientists about lung cancers found in animal studies of zopiclone. The lung cancer specificity supports causality.

There was one pair of studies that was neither clearly confirmatory nor negative. A large-scale survey screening many drugs with a questionable scheme for reusing controls for multiple tests and incorporating a questionable 2-year drug-to-cancer lag remarked no significant association of cancer with temazepam or zolpidem but did find significant associations with oxazepam and perhaps lorazepam, using $P < 0.01$ and relative risk > 1.50 as criteria⁶⁷. In that study, it was not always possible to control for smoking, and control for other confounders was crude and not well-standardized. A similar study added a possible association for phenobarbital⁶⁸.

To summarize the cancer epidemiology, the great majority of relevant studies have noted either small or large hazards for new cancers associated with hypnotics. Epidemiologic studies of hypnotics and cancer incidence have had many limitations, and some of these studies were not well-controlled for important confounders such as smoking and obesity, but the preponderance of evidence suggested a causal elevation of cancer incidence among those who take hypnotics.

The available clastogenicity data, animal data, randomized placebo-controlled clinical trials, and human epidemiology studies consistently, if not always conclusively, suggested that hypnotics likely cause human cancers and cancer deaths.

Hypnotics increase incidence of clinical depression

In combined clinical trials, participants randomized to hypnotics suffered 2.1 times as many incident (new) depressions as those randomized to placebo ($P < 0.002$)²³. These were not exacerbations of pre-existing depressions. These were depressions caused by the hypnotics. There are other data demonstrating worsening of depression with a wider variety of popular benzodiazepine and GABA agonists⁹. Treatment of insomnia by hypnotics causing comorbid depression stands in marked contrast to cognitive-behavioral treatment of insomnia, that has been shown to decrease comorbid depression⁶⁹.

Some studies have appeared designed to show that a hypnotic reduced depression scores among patients given an antidepressant known to cause insomnia^{70,71}. In the first of these studies, the benefit of the hypnotic for depression was not significant at week 4 after the investigators removed the rating scale items related to insomnia, whereas the week 8 benefit was only significant at the $P = 0.04$ level not correcting for multiple comparisons. In other words, using rigorous Bonferroni correction for multiple comparisons, the alleged benefit of hypnotic for depression symptoms was not significant. In the second study the authors more readily conceded that the hypnotic had no significant benefit for depression. These studies failed to rebut the evidence that hypnotics cause new depressions.

Depression is the major cause of suicide. Panic attacks are another risk factor for suicide⁹. Short-acting benzodiazepine agonists such as triazolam and zolpidem may cause withdrawal anxiety and even panic attacks during the daytime⁷². Suicide has been recently described as the 8th or 10th leading cause of death in the United States^{7,73}. Hypnotic use is associated with high rates of suicide^{25,55,74}. Indeed, comprehensive toxicological studies have found intoxicating abusable substances (mainly sedative-hypnotics) in a majority of suicides, often combined with alcohol in 30–40%⁹. Suicides due to overdoses have increased dramatically from 1999 to 2010 in the U.S.⁷⁵, but there have been an even larger number of deaths of undetermined manner in which suicide through overdose must be suspected⁷⁶. A very recent report estimated that in 2013 there were 7,000 overdose deaths related to anxiety and sleep medications⁷³, but this did not include all suicides in which the most rigorous toxicology shows a sedative or anxiolytic often mixed with alcohol to be present⁹. The adjusted odds rate for suicide was 4.2 among hypnotic users as compared to nonusers in one study of elderly people, whereas the odds were not elevated among anti-depressant users (tending to exclude depression and other comorbidities as confounders⁷⁷.) Prescription sleeping pill use was a stronger predictor of suicide attempts than insomnia symptoms in the National Comorbidity Survey Replication⁷⁸. In a large study from Taiwan, the adjusted suicide hazard ratio for “needing sleeping pills” was 11.1, whereas the hazard ratio for those reporting sleeping only 0–4 hours adjusted for sleeping pill use was only 3.5, and none of the hazard ratios for insomnia symptoms exceeded 2.0⁷⁹. Another national Taiwan study found increased suicides and attempts associated with zolpidem⁷⁴. The findings indicate that the association of suicides with hypnotic use cannot be entirely attributed to

confounders with reverse causality, since the association of hypnotic usage with depression is known to be largely caused by the hypnotics²³.

Zolpidem specifically has been implicated as a causal agent in a number of suicides, some of which involved kinds of dissociative behavior often attributed to zolpidem or to combined use of zolpidem with other drugs or alcohol⁸⁰. Impairments of cognition and judgment that may be caused by sleeping pills⁸¹ as well as hallucinations⁸², irrational behaviors^{75,83–85}, and behavioral disinhibition⁹ may all contribute to suicides, violence, and accidents, even among people who are not severely depressed.

Automobile crashes, falls, and other accidents are associated with hypnotics

Hypnotic drugs impair next-day alertness, motor skills, reasoning, and overall performance. Accidents of all sorts are associated with use of benzodiazepines and benzodiazepine agonists such as zolpidem^{86–88}. Most hypnotics impair automobile driving, as indicated by on-the-road controlled performance testing⁸⁹. This impairment in some instances exceeds the impairment produced by a blood alcohol concentration of 0.05%⁹⁰. Drivers’ ability to predict their own impairment is poor⁹¹. The use of hypnotics and other sedatives is strongly associated with on-the-road driver-at-fault crashes^{92–96}. In addition to accidents attributable to impaired coordination, impaired motor skills and loss of alertness, hypnotics may also lead to fatal crashes due to drug induced suicidal thinking, impaired judgment, or recklessness on the part of intoxicated drivers⁷. Some of these crashes result in deaths of passengers and other-vehicle occupants not themselves using hypnotics, but the other-vehicle deaths are not attributed to the hypnotics on death certificates.

One study showed that use of benzodiazepines and “Z” hypnotics was increased among victims of homicide as well as among the homicide perpetrators⁹⁷. Thus, both through bad driving and homicides, hypnotics result in deaths that have not been accounted directly as deaths from these hypnotic drugs.

It is well known that falls and accidental injuries are strongly associated with hypnotic usage, in particular hip fractures among aging patients^{98–106}. Hip fracture is a sometimes-lethal injury. The preponderance of studies indicates a true association of the use of hypnotics and falls, that is thought to be due to the properties of benzodiazepine agonists in inhibiting psychomotor skills and in causing weakness, slowed reflexes, and impaired judgment, especially less than 8 hours after ingestion. After taking a hypnotic at bedtime, older people may get up during the night, e.g., to visit the bathroom, when the pharmacologic impairment from a hypnotic is near-maximum and is combined with impairments from sleepiness.

A nursing-home study challenged these conclusions, arguing that it was insomnia, not hypnotics, that was associated with falls. This study did not appear to control for confounding sleep apnea, Alzheimer’s disease, or cognitive-behavioral disorders¹⁰⁷. It should be conceded that confounders are likely have some influence on risk ratios associating hypnotics with accidental injuries, but the scientific consensus suggests that the association is nevertheless partly causal, based in part on controlled trials showing hypnotic

impairments of driving and other forms of psychomotor performance. A causal element is inferred by the majority of authorities.

Safe doses of hypnotics for target populations are unknown

Animal studies indicate that some individuals in an animal research sample may succumb to a lethal hypnotic-drug effect at doses as low as one-fifth that which is universally lethal¹⁰⁸. Variations in susceptibility in a human population varying in age, gender, genetics, and health status is likely to be greater than that in a sample of laboratory animals. The minimum lethal dose of hypnotic drugs in humans is unknown, that is, the dose that might produce fatal respiratory arrest in one person out of 1000 in a representative population or one in 10,000. So many billions of hypnotic doses are prescribed yearly in the U.S. that one death per 10,000 doses would yield over 100,000 deaths per year. Moreover, there are no human dose-response data and very little animal data concerning what doses of hypnotics may be lethal in the presence of opiates, other sedatives, alcohol, aging, obesity, COPD, and other comorbidities. Yet most recognized hypnotic-related deaths are observed in the presence of such additional factors. More study is needed to establish safe doses of hypnotics (if any) when taken with other medications and in the presence of potential comorbidities. As for aging, the consensus of the American Geriatrics Society is that hypnotics should not be given to elderly patients in any dose¹⁰⁹.

Contributory factors combined with hypnotics could cause covert deaths

There is a vast discrepancy between the hundreds of thousands of yearly hypnotic-associated deaths implied by the high epidemiologic hazard ratios and the mere thousands of yearly death certificates in which a hypnotic is listed among the causes of death. Below are presented some of the possible explanations for this discrepancy.

Obesity and aging exacerbate hypnotic risks

Obesity and aging are perhaps the two most important risk factors for sleep apneas, that is, brief cessations of breathing during sleep¹¹⁰. Sleep apneas occurs at least a few times per hour in the majority of adults over age 40 years and in a great majority of those over age 65^{110,111}. If the duration of a sleep apnea before arousal becomes excessively prolonged, e.g., by a hypnotic, death could result. Even apart from apneas caused by obesity, mechanical problems produced by obesity may impair ventilation. Thus, hypnotic-related hazard ratios are higher among obese patients (see Geisinger Health study supplement Tables 2 and 7¹⁶.) Since there is no evidence that the huge increase in hypnotic hazards among obese patients can be attributed overdoses alone, it appears that obesity predisposes to covert hypnotic-related deaths, probably by prolonging apneas. The contributing role of combining hypnotics with opiates, other sedatives, and alcohol has already been discussed and is further discussed below. It is plausible that among susceptible patients, combinations of aging, obesity, sleep apnea, hypnotics, opiates, other sedatives, and alcohol could produce quiet respiratory cessations followed by cardiac cessation and death even without any ingested doses above common medical practice being taken. In effect, the “overdose” comes from the overdose of contributory factors along with a hypnotic, not from an excessive dosage of a

hypnotic considered by itself. Recall that the American Geriatrics Society does not approve of administering hypnotics to elderly patients in any dose¹⁰⁹, though a substantial portion of all hypnotic prescriptions go to elderly patients.

Prescription and non-prescription opiate use increase hypnotic risks

The use of opiates has become increasingly common in recent years¹¹². Opiates are respiratory suppressants that (like pentobarbital) in overdose can produce respiratory arrest and cardiac arrest. Among patients taking both benzodiazepines and opiates, a remarkable 75% were found to have sleep apnea, and causality was suggested by significant dose-response correlations both for the opiates and for the benzodiazepines¹¹³. In some patients, this combination of benzodiazepine and opiate causes hypoxemia (low oxygen)¹¹⁴. Our sleep clinic has recorded polysomnographic data from patients who suffered profound almost continuous apnea with severe hypoxemia due to combinations of hypnotics and opiates. Recall that it is understood on a molecular level how benzodiazepine agonists and opiates combine to suppress firing of respiratory neurons that are necessary to breathe. Patients receiving a combination of benzodiazepines and opiates have increased mortality¹¹⁵⁻¹¹⁷. The combination of opiates and benzodiazepines has caused a growing overdose problem in emergency rooms¹¹². Moreover, the most serious overdose problems are seen when opiates and benzodiazepines are combined with alcohol in older patients, reflecting combined effects of opiate, benzodiazepine, alcohol, and aging^{6,117}.

It may be relevant that close to 70% of hospice patients were taking an opiate and an anxiolytic or hypnotic in the last week of life¹¹⁸. This is not evidence by itself whether this combination influences the survival of hospice patients, nor is the author commenting on the ethics of combining such drugs in a genuine hospice situation. However, most patients given hypnotics and opiates have not consented to hospice management.

Quiet deaths from hypnotics with contributory factors go undetected by medical examiners

In many combined-sedative deaths, the individual drug concentrations present in blood may appear within customary therapeutic ranges. Even if a patient is undergoing cardio-respiratory monitoring at the time when respiratory cessation followed by cardiac cessation occurs, there is usually no way of determining whether the fatal respiratory cessation was due to hypnotic drugs in combination with various contributory factors. Especially when death occurs quietly at night (for example, death of an elderly obese patient known to have various comorbidities,) there usually is no autopsy. Physicians signing the death certificates may be tempted to list a cardiac event or a stroke or some long-standing comorbidity as the cause of death without recognizing when hypnotic-induced respiratory suppression was the precipitant.

The press described a highly distinguished example of how the cause-of-death is often declared after U.S. Supreme Court Justice Scalia died unexpectedly at night. According to numerous news reports and sheriff's documents, Justice Scalia's appearance was that of a person who had peacefully stopped breathing at night. There was no sign of agitation due to cardiac pain, nor had Justice

Scalia complained of cardiac symptoms before going to bed. Justice Scalia might have been taking hypnotics and opiates for the jet lag and pain he was known to be suffering when he arrived at a hunting lodge that routinely gives each guest a free bottle of wine. By the bedside, his CPAP machine for control of sleep apnea was not connected, perhaps because he was too excessively sedated to connect his CPAP device or because of problems related to the 4400 feet altitude. Without ever viewing the deceased or his bedroom, much less determining what hypnotics, opiates for pain, and alcohol Justice Scalia had consumed, a local official was encouraged by Justice Scalia's physician (thousands of miles away) to declare heart attack as the cause of death. Without an autopsy, we will never know if this death was precipitated by hypnotics or opiates and alcohol or if there was a heart attack. Even if a physician suspects that a hypnotic had a role, the physician has little motivation to list the hypnotic as a cause of death when it would be hard to prove and may reflect negatively on the physician prescribing that hypnotic.

Along the same lines, when hypnotics cause infection, cancer, depression, falls or other accidents, or murder, hypnotics are rarely listed among the causes of death. These patterns along with quiet respiratory deaths may explain why epidemiology shows much higher risks of death associated with hypnotics than the death certificates document. Nevertheless even the numbers documented in death certificates are much too high to be acceptable.

Commonly-prescribed hypnotics are used in unsafe combinations

Zolpidem, reportedly the most commonly-prescribed hypnotic in the U.S., with an estimated 40 million outpatient prescriptions in 2013¹¹⁹, ranked first for emergency department visits among psychotropic drugs according to CDC data^{119,120}. According to the Agency for Healthcare Research and Quality (AHRQ) data, 68% of zolpidem patients were sustained users (three or more prescriptions), and of those 22% were also sustained users of opioids¹¹⁹. Note that recent CDC guidelines recommend against use of benzodiazepine agonists with opiates¹²¹. Although the FDA had recommended that women use only 5 mg or 6.25 mg of zolpidem, only 5% of women and 10% of elderly were prescribed these low doses¹¹⁹. Moreover, 23% of patients with sustained use took another drug targeting the same receptors. A high percentage were depressed, as indicated by 34% of sustained zolpidem users also receiving antidepressants¹¹⁹. Recall also that the American Geriatrics Society recommended avoidance of any use of hypnotics for elderly patients¹⁰⁹, though many receiving hypnotics are elderly

Hypnotics cause withdrawal insomnia, anxiety, panic, and epilepsy

It has been well known since they came into use over a century ago that hypnotics and similar sedatives are addicting drugs, frequently eliciting tolerance, physical dependence, and withdrawal reactions. Most of the benzodiazepine agonist hypnotics and even suvorexant are controlled like addicting drugs by the U.S. Drug Enforcement Agency (DEA). Withdrawal from benzodiazepine agonists can cause insomnia, anxiety, agitation, confusion, and

panic and even more severe somatic symptoms such as seizures and death in extreme cases^{24,72,121,122}. In addition, some of the short-acting sedatives such as triazolam and zolpidem may sometimes cause anxiety or agitation during the day following administration before the previous bedtime. Dr. Kripke has seen two patients taking triazolam who developed daytime panic attacks that remitted upon triazolam withdrawal and recurred upon re-challenge. There is also evidence that prolonged use of hypnotics may lead to lasting insomnia, as a consequence causing patients who withdrew from hypnotics to sleep worse than patients who had been randomized in parallel clinical trials to placebos²⁴. How long this withdrawal insomnia might persist has never been adequately defined.

In another example of sedative withdrawal leading to hyperexcitability, there is a report that benzodiazepine use and withdrawal may result in lasting increased epilepsy¹²³.

Relationship of hypnotics to insomnia, long sleep, and short sleep

A pioneering large epidemiological study by the American Cancer Society study conducted over 50 years ago showed an increased risk of death following hypnotic use. The Cancer Prevention Study I (CPSI) obtained questionnaires in 1958 from over 1,000,000 participants and reliably followed up their death or survival for 6 years¹²⁴. The data showed that both long and short sleep predicted elevated mortality (with 7 hours associated with minimal mortality for each age group). This study (often replicated) raised scientific doubt whether there is medical value to increasing reported sleep duration of an adult beyond 7 hours, though it also demonstrated that many adults reporting more than 7 hours of sleep were taking sleeping pills. Sleep durations below the population median are partly attributable to inherited traits, so whether there would be any health benefit in sedating people with short sleep durations to sleep longer remains to be demonstrated. A small objective study of sleep duration recorded by wrist activity suggested increased mortality above 390 minutes of actual sleep (which is greater than the current median sleep of American adults studied with similar technology¹²⁵.) In the CPSI data, self-reported insomnia had little or no additional mortality effect beyond hours of sleep, although insomnia was moderately associated with short sleep. In contrast, reported sleeping pill use was associated with about 50% increased mortality after controlling for age, gender, reported sleep duration, and reported insomnia¹²⁶. This was statistically a highly significant result in a million participants, but uncertainty about what participants meant by taking "sleeping pills" "Often" in terms of drug type and frequency demanded more study. The American Cancer Society performed a second Cancer Prevention Study (CPSII) with participants completing over 1.1 million questionnaires in the fall of 1982. CPSII used more explicit questions about sleep duration, insomnia, and "prescription sleeping pills." After controlling simultaneously for 32 covariates and confounders such as insomnia and sleep duration in Cox Proportional Hazards models, results again showed that use of hypnotics was associated with elevated mortality not attributable to major confounders such as cigarette smoking. Indeed, the mortality risk associated with

taking “prescription sleeping pills” was surprisingly comparable to that associated with smoking a pack of cigarettes a day⁵⁵.

Benefits of hypnotics: minimal

Popular prescribed hypnotics fail objectively to increase sleep significantly even at high doses

In an authoritative National Institutes of Health (NIH)-sponsored meta-analysis of controlled trials including unpublished trials¹²⁷, Buscemi and colleagues found that although non-benzodiazepine zolpidem-like drugs [“Z-drugs”] shortened sleep onset latency by an average of 12 minutes (9–17 min, 95% CI), according to objective polysomnograms, these hypnotics increased total sleep time by only 11 minutes (-1 to 23 min, 95% CI, NS). That is, these “Z” drugs produced no substantial statistically-reliable increase in total sleep, even at doses higher than currently recommended. Most of the meta-analyzed studies of zolpidem used doses of 10 mg or more (as high as 30 mg)¹²⁷, and most of the studies of zopiclone used 7.5 mg doses or more (containing more eszopiclone than any dose approved in the U.S.). The FDA-approved recommended initial zolpidem dosage for most patients is now 5 mg (6.25 mg for the sustained-release form¹²⁸.) Zolpidem and zolpidem-like drugs constitute the bulk of the current U.S. hypnotics market. Based on all available clinical studies, these lower doses would objectively increase sleep little if at all¹¹⁹. Indeed, the primary zolpidem manufacturer advised the FDA that the 5–6.25 mg dosages were generally ineffective³². The newly-recommended 1-mg dosage of eszopiclone is similarly ineffective^{129,130}. Patients typically report more increase in sleep than is measured objectively, but even this self-reported “improvement” at above-recommended doses (which is not supported by objective measurement) is a mere 32 minutes. (26–38 minutes, 95% CI)¹²⁷. The discrepancies between objective and patient-subjective data may be attributable to the amnesic properties of hypnotics, erasing patients’ memories of how much time they are awake in bed. In conclusion, the FDA-recommended doses of the most popular benzodiazepine agonists are virtually ineffective for objectively increasing sleep. Older benzodiazepines are not much more effective, if at all.

A new Comparative Effectiveness Review sponsored by the U.S. AHRQ has recently examined the Management of Insomnia Disorder, largely referring to chronic insomnia¹³¹. As a prepublication Peer Reviewer of this report, I was and still remain very critical of its limitation to mainly-subjective data that are known to give a rosier evaluation of hypnotic effects than objective evaluations, its focus on published reports that are known to be commonly biased towards reporting favorable drug results^{132,133}, and the AHRQ report’s incomplete attention to adverse effects. Nevertheless, it is striking that the AHRQ study found that the strongest evidence for treatment efficacy was with the cognitive-behavioral treatment of insomnia. The evidence for short-term efficacy of zolpidem and eszopiclone in high doses was considered less sufficient, and evidence for efficacy of other hypnotics was judged to be almost entirely insufficient. Moreover, by its clinical trial selection criteria, this Review found essentially no evidence for efficacy of the very low doses of zolpidem and eszopiclone currently recommended by the FDA for most patients, because higher doses appeared unsafe to FDA. In short, the AHRQ study presented no reason why hypnotics are needed, since cognitive-behavioral treatment of insomnia is better and is available even on the internet.

Moreover, the AHRQ Review found evidence for increased adverse effects with hypnotics compared to placebo, including hypnotic adverse effects of concern (their selection of studies highlighted fractures and dementia.) The Review found mention of adverse effects virtually absent for the cognitive-behavioral treatment studies¹³¹. Although the Comparative Effectiveness Review found insufficient studies to estimate the comparative effectiveness of hypnotics versus cognitive-behavioral treatments, when it reviewed potential harms, there was no contest. Moreover, controlled trials reviewed above prove that hypnotics cause comorbidities such as infection and depression and driving impairments, whereas cognitive-behavioral treatment has been found to decrease medical comorbidities such as depression⁶⁹.

Hypnotics fail to improve next-day performance or general health

Based on manufacturers’ advertising, patients expect that a hypnotic will improve their function and performance the following day. In fact, the truth is just the opposite. In 1982, two sleep experts received partial support from a hypnotics’ manufacturer to survey daytime performance literature about hypnotics and found, “Drug-related improvement in performance was not found, and, in comparing active drug to placebo, it is clear that all hypnotics, at some doses, produce decrements in performance the next day⁸¹.” Since 1982, the author has been looking for objective evidence that hypnotics improve the performance of insomnia patients. Decades later, no evidence that GABA-agonist hypnotics improve objective daytime performance in treating insomnia has been located. If there is a proven significant effect, it is to make performance worse^{89,134}. Incidentally, the AHRQ Comparative Effectiveness Review mentioned no objective evidence of functional benefits from hypnotic drugs¹³¹. On average, most hypnotics make patients more sleepy the next day, not more fully awake.

After 34 years, the author is still looking for evidence of objective functional benefit. In a recent letter to *Sleep Medicine*, readers were asked to inform us if “any U.S.-licensed hypnotic ever objectively improved any aspect of insomnia patients’ daytime function or any aspect of general health¹³⁵.” So far, nobody has informed me of any such evidence.

Hypnotic drugs are prescribed to patients without valid clinical indication

According to the U.S. National Ambulatory Medical Care Survey, insomnia is a stated reason for a patient’s visit in less than one quarter of office visits where a hypnotic is prescribed², but for most of these drugs, insomnia could have been the only approved indication. Moreover, no diagnosis of any sleep disorder at all is made on 35% of office visits when a hypnotic is prescribed, and of the 65% of such patients who are diagnosed with a sleep disorder (such as hypersomnia and most forms of sleep apnea), often a hypnotic would be contraindicated². Other data have likewise shown that hypnotics are commonly prescribed for patients who have no diagnosis or complaint of insomnia^{126,136,137}. Thus, hypnotics are routinely being prescribed without any apparent valid indication in as much as three quarters of the cases. Moreover, it appears from the data reviewed above that in most cases or at least a great many, hypnotics are prescribed despite a specific contraindication. For example, in the 2015 Beers criteria of the American Geriatrics

Society, the hypnotics of concern in this presentation are all listed as drugs to avoid¹⁰⁹. It would be fanciful thinking to imagine that addicting hypnotics could be generally beneficial as usually prescribed: without indication and despite specific contraindications.

Manufacturers misrepresent hypnotic benefits in direct-to-consumer advertising

An instructive example is a 2006 advertisement representing that “[eszopiclone] provides a full night of sleep (7 to 8 hours).” An equivalent claim was made in a 2007 eszopiclone-hypnotic print advertisement titled “Sleep the night and seize the day. . . A better tomorrow begins tonight.” In the scientific study cited by both advertisements as evidence¹³⁸, the average sleep of patients receiving eszopiclone 2 mg was 382 minutes (6 hours, 22 min) and for 3 mg, it was 412 minutes (6 hours, 52 min). The clinical results cited did not support the manufacturer’s claims to “a full 7 to 8 hours of sleep,” even though the 2 mg and 3 mg doses then studied were greater than the currently-recommended starting doses.

As for the manufacturer’s advertised benefits of “seizing the day,” and a “better tomorrow,” the eszopiclone manufacturer’s study demonstrated no significant objective improvement in measured next-day daytime performance or accomplishment. Specifically, an objective morning performance test did not demonstrate significantly better performance with eszopiclone than with placebo¹³⁸.

It is not my intention to imply that misrepresentation in consumer advertising has come only from a single manufacturer. There have been many examples with other hypnotics.

Summary of benefits and risks

The evidence is clear: the most popular hypnotics offer little to no benefit to patients in recommended doses. This statement applies most specifically to zolpidem, temazepam, eszopiclone, zaleplon, triazolam, flurazepam, quazepam, and barbiturates used for sleep. The most recent American Academy of Sleep Medicine’s Clinical Guideline for Management of Chronic Insomnia¹³⁹ stated that the primary goals of treatment of insomnia should be to increase sleep quantity and to enhance daytime function. To the contrary, popular hypnotics do not increase objective sleep substantially (if at all.) and for many patients, hypnotics cause substantial objective next-day functional impairment. In confirmation, FDA records show that the lead manufacturer of zolpidem (the most commonly-prescribed hypnotic) stated that the FDA-recommended dosage was ineffective³². The National Ambulatory Medical Care Survey indicated that over three quarters of hypnotic prescriptions are given to patients who do not even come to the physician for insomnia². Yet the specified hypnotics do not substantially improve objective sleep or objective daytime performance and have no known objective benefits for any aspect of general health.

Contrasting with the questionable benefits, the popular benzodiazepine agonists in the U.S. are associated with increased mortality hazards, comparable to the hazards of barbiturates. Medical examiner data document that over 10,000 deaths every year are directly caused by and attributed to hypnotic drugs, and there is substantial evidence that hypnotics cause additional covert respiratory depression, suicides, infection, cancer, accidents, and other disorders that lead to a far larger number of deaths as well as to non-fatal morbidities and suffering. Use of hypnotics kills large numbers of Americans yearly; however, the exact number of deaths caused by hypnotics cannot be estimated from medical examiner data alone¹¹², because most of the deaths produced by hypnotics are covert or indirect due to hypnotic-induced or hypnotic-exacerbated morbidities such as respiratory depression, infection, accidents, etc.

This presentation focused primarily on zolpidem, temazepam, eszopiclone, zaleplon, triazolam, flurazepam, quazepam, and barbiturates used for sleep (such as pentobarbital, amobarbital, and secobarbital). These specified drugs have little or no benefit for insomnia, and are commonly not even prescribed for presenting insomnia or other approved indications. These drugs were the focus because each has been shown epidemiologically to be associated with high mortality hazards¹⁶. There are other hypnotics approved for treating insomnia in the U.S.: specifically, diphenhydramine, ramelteon, doxepin, and suvorexant. Moreover, other drugs very commonly prescribed for sleep include trazodone (off label) and melatonin (unregulated). This presentation was not focused on these other drugs used as hypnotics, either because the epidemiologic and controlled-trials data have not been sufficient to assess their risks as hypnotics or because these drugs are approved and may be effective for indications other than insomnia.

In the supplement to the Geisinger Health System study, the best-estimate extrapolation from the data suggested that 300,000 – 500,000 deaths each year in the U.S. were associated with hypnotic usage¹⁶. The risks of under-estimation in this study were thought to be as great as the risks of over-estimation. Since this estimate was derived from risk ratios fully-adjusted for confounders, it is plausible that most of the association was causal.

This hypnotic mortality risk is almost comparable to that of cigarette smoking and many-fold greater than the risk to Americans of violent death.

Hypnotic drugs	300,000–500,000 U.S. deaths per year ¹⁶
Cigarettes	560,000 U.S. deaths per year ¹⁴⁰
Murders	14,196 U.S. deaths in 2013

The number of hypnotic-associated deaths may be almost comparable to the number of deaths attributed to cigarette smoking (560,000), cancer (585,000), or heart disease (611,000).

Apart from hypnotics, the preferred treatment for insomnia is the cognitive-behavioral treatment of insomnia, which appears to be more effective in the long run, better for comorbidities, and safer¹³¹. Cognitive-behavioral therapy can be effectively provided through written materials, internet training programs, and brief group therapies. It has been argued that cognitive-behavioral treatment saves money, compared to hypnotics¹⁴¹.

Circadian rhythm timing disorders can cause the biologic propensity for sleep to be either delayed (causing trouble falling asleep and trouble waking in the morning) or too advanced (causing evening sleepiness and early awakening). It is unclear how often the circadian rhythm timing disorders have a more important role in insomnia than the cognitive-behavioral elements, but one estimate suggests that “eveningness” may be associated with trouble falling asleep in as much as one quarter of the adult population¹⁴². When circadian timing issues are important, properly timed bright light treatment can be a safe, effective, and inexpensive non-drug treatment that also has benefits for comorbidities such as depression, but more clinical trials are needed to better define the applicability of bright light treatment for insomnia.

A very recent Clinical Practice Guideline from the American College of Physicians has recommended that cognitive behavioral therapy be the initial treatment for chronic insomnia disorder. Because of only very weak evidence for benefits and more impressive evidence for occasional serious harms, the Guideline left uncertain whether hypnotics were ever wise as a secondary

treatment for short-term use, and the Guideline did not recommend long-term hypnotic prescribing at all¹⁴³.

Competing interests

Since 1979 publication of hypnotics’ epidemiology from the American Cancer Society CPSI study, the author has been a frequent critic of hypnotics risks and benefits, especially through his non-profit internet web site, www.DarkSideOfSleepingPills.com, that offers readers additional information and references about hypnotics. Dr. Kripke’s family owns non-controlling stock and options in a large conglomerate that in turn invested a tiny percentage of its capital in Sanofi-Aventis and Johnson and Johnson stock. The author has advised the USA Food and Drug Administration to take certain actions regarding hypnotics (Petition available at <http://www.regulations.gov#!docketDetail;D=FDA-2015-P-3959>), and related litigation may arise. The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, other stock ownership or options, expert testimony, grants or patents received or pending or royalties. No writing assistance was utilized in the production of this manuscript.

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Appendix A: Epidemiologic Studies of the Mortality Risks of Hypnotic Drugs

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This report is important and over due, and most likely would not be published in a journal that accepts advertising from pharmaceutical companies. The author is careful NOT to confuse association with causation. References are complete and up-to-date.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 23 May 2016

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Jerome Siegel

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This paper pulls together evidence from Dr. Kripke's own work and subsequent work, which indicate that the use of benzodiazepines and perhaps other sleeping pills is causing thousands, perhaps hundreds of thousands of deaths annually in the United States. He reviews the complete lack of evidence for any positive health effect of the use of these drugs. This is especially striking because drug companies sponsor a considerable amount of research on their sleeping pills and would undoubtedly publicize any data indicating positive health or lifespan effects – but there do not appear to be any. Kripke also points out the effectiveness of cognitive behavioral therapy for insomnia. This well studied treatment is less expensive, without any known deleterious effects on lifespan or health and produces a long-lasting reduction in insomnia. The effectiveness of cognitive behavioral therapy in the treatment of insomnia contrasts with the miniscule (0-20 min) increase in sleep time produced by sleeping pills, followed by a considerable withdrawal effect if the patient stops taking the pills.

Minor suggestions include the following:

1. I would delete the discussion of Judge Scalia's death. Although it gets one's attention, without knowing what Scalia was taking and without any documentation of the cause of death, it does more harm than good to the impact of the paper.
2. On page 10, I would delete the paragraph on prescriptions without valid clinical indication. I guess that in many cases the prescribing physician would just say he forgot to document the need. I do not doubt that Dr. Kripke is bringing attention to an important issue, but it is not persuasively presented, in contrast to the rest of his argument.
3. Small typo under "Obesity and aging exacerbate hypnotic risks:" "can be attributed overdoses "

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response 30 May 2016

Daniel F. Kripke, University of California, San Diego, USA

The kind reviews and useful contributions from Dr. Siegel and Dr. Phillips are much appreciated.

Regarding the paragraph about the death certificate of Justice Scalia, debate about his cause of death and concern about the lack of autopsy received considerable press attention in major media in the United States. The process by which a rural judge decided what cause of death to record on the death certificate was uniquely well documented by the press. This illustrated how a death that could have been due to an overdose might not be explored and the overdose possibility might not be recorded. Knowing what the patient's primary doctor had or had not prescribed would not resolve the issue of what drugs were or were not taken. This paragraph was intended to exemplify how we may indeed lack adequate documentation of the real cause of death when the plausible possibility of death caused by a hypnotic is not acknowledged on a death certificate.

Regarding hypnotic prescriptions without a recorded diagnosis of insomnia, indeed the prescribing physician might just say that forgetting to document the insomnia was an oversight, but it is implausible that oversight is the explanation for such a large percentage of total hypnotic prescriptions. If lack of indication is usually an oversight, where is the proof? When I was a medical student in the 1960's, I was trained that a hypnotic drug should be part of preprinted routine admission orders, and I have verified that routine admission orders for hypnotics are still preprinted in distinguished academic training hospitals in 2016. If we are training young doctors to prescribe a hypnotic without asking the patient whether that patient is experiencing trouble sleeping and without weighing the benefits and risks for the individual, it is plausible that habit persists in primary care. My impression is that prescribing doctors often do not ascertain that the patient has diagnostic criteria for insomnia, and in many cases, physicians know that the patient has no trouble sleeping. The physician might be trying to treat depression or to supplement opiates, but both uses are contraindicated. The physician might be treating some condition further afield such as hypertension or might be intentionally trying to achieve a placebo effect. There were studies documenting such practices several decades ago (references 126 and 136), but I know of no adequate study of 21st century U.S. outpatient hypnotic prescribing intentions. The manufacturers of both zolpidem and suvorexant have informed the FDA that the currently-FDA-mandated recommended doses are ineffective. It is tempting to infer that the FDA countenances the use of

ineffective hypnotic doses as placebo implements of the bedside manner, without evidence that benefits outweigh risks of potentially addicting or lethal placebos.

Competing Interests: Please see disclosure in the article.
